Amendments to the Specification:

Please make the following clarifying amendments to the specification.

Please replace the paragraph starting at page 1, line 6, with the following rewritten paragraph:

This application is a Continuation Application of U.S. Application Serial Number 09/714,438, filed November 17, 2000, which claims priority [from] to [United States provisional patent application] U.S. Provisional Application Serial No. 60/166,652, filed [19] November 19, 1999, and [United States provisional patent application] U.S. Provisional Application Serial No. 60/224,362, filed [11] August 11, 2000.

Please the replace paragraph starting at page 3, line 17, with the following rewritten paragraph:

Classic ISCOMS are formed by [combination of] a sterol such as cholesterol, saponin, phospholipid, and immunogens, such as viral envelope proteins. ISCOM matrix compositions (known as ISCOMATRIX™) are formed identically, but without viral proteins. ISCOMs appear to stimulate both humoral and cellular immune responses. ISCOMs have been made with proteins from various viruses, including HSV-1, CMV, EBV, hepatitis B virus (HBV), rabies virus, and influenza virus, see for example, I.G. Barr *et al., Adv. Drug Delivery Reviews*, 32:247-271 (1998). It has been observed that where naked DNA or polypeptides from infectious agents are poorly immunogenic when given by themselves, inclusion within ISCOMs has increased their immunogenicity. Various proteins formulated with ISCOMs have been shown to induce CTL, mainly in rodent models. Berzofsky, (1991), *Biotechnol. Ther.* 2:123-135; Hsu *et al.*, (1996) *Vaccine* 14:1159-1166; Lipford *et al.*, (1994), *Vaccine* 12:73-80; Mowat *et al.*, (1991), *Immunology* 72:317-322; Osterhaus *et al.*, (1998), *Dev. Biol. Stand.* 92:49-58; Rimmelzwaan *et al.*, (1997), *J. Gen. Virol.* 78(pt.4):757-765; Sambhara *et al.*, (1998), *J. Infect. Dis.* 177:1266-1274; Sambhara *et al.*, (1997), *Mech. Aging Dev.* 96:157-169; Sjolander *et al.*, (1997), *Vaccine* 15:1030-1038; Sjolander *et al.*, (1998), *J.*

Leukoc. Biol. 64:713-723; Takahashi *et al.*, (1990), *Nature* 344:873-875; Tarpey *et al.* (1996), *Vaccine* 14:230-236; Trudel *et al.*, (1987), *Vaccine* 10:107-112; Verschoor *et al.*, (1999), *J. Virol.* 73:3292-3300; Villacres-Eriksson, (1995), *Clin. Exp. Immunol.* 102:46-52; Zugel *et al.*, (1995), *Eur. J. Immunol.* 25:451-458.

Please replace the paragraph starting at page 5, line 3, with the following rewritten paragraph:

In work leading up to the present invention, the inventors have developed an immunogenic complex based on the electrostatic association of an antigen of HCV and an [organic carrier, such as] organic complex, particularly an adjuvant. This electrostatic association permits co-delivery of the antigen and the organic carrier to the immune system, for the purpose of inducing an immune response, particularly a cytotoxic T-lymphocyte response, to the antigen.

Please replace the paragraph starting at page 5, line 18, with the following rewritten paragraph:

One aspect of the present invention relates to an immunogenic complex comprising a negatively charged organic [carrier] complex and a charged antigen, which organic [carrier] complex and antigen are electrostatically associated, [and] wherein the [charged antigen is a polyprotein of Hepatitis C Virus (HCV) or a fragment thereof, or a fusion protein comprising said polyprotein or a fragment thereof] organic complex comprises a saponin and a sterol, and wherein the charged antigen comprises one or more polypeptides from a region of Hepatitis C Virus (HCV), selected from the group consisting of core, E1, E2, NS3, NS4a, NS4b, NS5a and NS5b.

Please replace the paragraph starting at page 5, line 24, with the following rewritten paragraphs:

[Preferably, the polyprotein is the core protein of HCV] In one embodiment, the charged antigen may be a fusion protein comprising said HCV polypeptide.

Preferably, the polypeptide is the core protein of HCV, or a fragment thereof of at least 10 contiguous amino acid residues that defines at least one T-cell epitope of the HCV polypeptide.

Please replace the paragraph starting at page 5, line 26, with the following rewritten paragraph:

Another aspect of the present invention more particularly provides an immunogenic complex as described above, wherein the charged organic [carrier is a negatively charged organic carrier] complex is an adjuvant.

Please replace the paragraph starting at page 5, line 30, with the following rewritten paragraph:

Yet still another aspect of the present invention provides an immunogenic complex as described above, wherein the [charged] organic [carrier]complex is a naturally negatively charged adjuvant. In another aspect, the organic complex may be modified to increase the degree of its negative charge.

Please delete the paragraph starting at page 6, line 1, in its entirety.

Please replace the paragraph starting at page 6, line 7, with the following rewritten paragraphs:

A further aspect of the present invention relates to a vaccine composition comprising as the active component an immunogenic complex comprising a negatively charged organic [carrier] complex and a charged antigen, which organic [carrier] complex and antigen are electrostatically associated, [and]wherein the [charged antigen is a polyprotein of Hepatitis C Virus (HCV) or a fragment thereof, or a fusion protein comprising said polyprotein or a fragment thereof,] organic complex comprises a saponin and a sterol, and wherein the charged antigen comprises one or more polypeptides from a region of Hepatitis C Virus (HCV), selected from the group consisting of core, E1, E2, NS3, NS4a, NS4b, NS5a and NS5b, together with one or more pharmaceutically acceptable carriers and/or diluents.

In one embodiment, the charged antigen may be a fusion protein comprising said HCV polypeptide.

Please replace the paragraph starting at page 6, line 15, with the following rewritten paragraph:

Preferably, the [polyprotein] polypeptide is the core protein of HCV, or a fragment thereof of at least 10 contiguous amino acid residues that defines at least one T-cell epitope of the HCV polypeptide.

Please replace the paragraph starting at page 7, line 7, with the following rewritten paragraph:

As described further below, the immunogenic complexes of the present invention may include, as the charged antigen associated with the charged organic [carrier] complex, an HCV protein such as an HCV Core nucleocapsid protein, a nonstructural protein, the E1 envelope protein, the E2 envelope protein, immunogenic fragments of any of such proteins, or combinations of such proteins. Such fragments generally include polypeptides comprising epitopes recognizable by T cells. Preferred fragments comprise those fragments which are immunogenic when provided by themselves, or when included in an immunogenic complex

of the present invention. As used throughout this specification, the term "polyprotein of HCV" or "HCV protein" is intended to include the full length protein as well as polypeptide fragments. The HCV protein may also be present in the immunogenic complexes of the present invention as fusion proteins, depending on which method of expression of the HCV protein is chose. The sequences for these polypeptides and proteins are known (see, e.g., U.S. Patent No. 5,350,671). The invention also provides polypeptides that are homologous (i.e., have sequence identity) to these fragments. Depending on the particular fragment, the degree of sequence identity is preferably greater than 50% (*e.g.*, 60%, 70%, 80%, 90%, 95%, 99% or more). These homologous polypeptides include mutants and allelic variants of the fragments.

Please replace the paragraph starting at page 10, line 29, with the following rewritten paragraph:

Accordingly, one aspect of the present invention relates to an immunogenic complex comprising a negatively charged organic [carrier] complex and a charged antigen, which organic [carrier] complex and antigen are electrostatically associated, wherein the [charged antigen is a polyprotein of Hepatitis C Virus (HCV), preferably the core protein of HCV, or a fragment thereof, or a fusion protein comprising said polyprotein or a fragment thereof] organic complex comprises a saponin and a sterol, and wherein the charged antigen comprises one or more polypeptides from a region of Hepatitis C Virus (HCV), selected from the group consisting of core, E1, E2, NS3, NS4a, NS4b, NS5a and NS5b.

Please replace the paragraph starting at page 11, line 8, with the following rewritten paragraph:

Reference to a "charged" organic [carrier] complex or antigen should be understood as a reference to an organic [carrier] complex or antigen which exhibits an overall positive electrical charge or an overall negative electrical charge. By "overall" is meant the summation of the individual positive and negative charges which a given molecule comprises.

Where the summation of the individual positive and negative charges results in overall electrical neutrality, the molecule is not regarded as "charged" within the context of the present invention. [Preferably, the organic carrier comprises an overall negative charge.]

Please replace the paragraph starting at page 11, line 21, with the following rewritten paragraph:

Reference to "electrostatically associated" is a reference to the organic [carrier] complex and the antigen being linked, bound or otherwise associated by means which include electrostatic interaction. Accordingly, it should be understood that in some instances the electrostatic interaction will be the only attractive force which results in complexing of the antigen and the organic carrier. However, in other instances the formation of the electrostatic interaction may also lead to, or be associated with, the formation of other interactive forces.

Please replace the paragraph starting at page 13, line 31, with the following rewritten paragraph:

Moreover, the polypeptide may be derived from any of the various known HCV strains, such as from strains 1, 2, 3 or 4 of HCV. A number of conserved and variable regions are known between these strains and, in general, the amino acid sequences of epitopes derived from these regions will have a high degree of sequence homology, e.g., amino acid sequence homology of more than 30%, preferably more than 40%, when the two sequences are aligned. Thus, for example, the term "Core" polypeptide refers to the native Core protein from any of the various HCV strains, as well as Core analogs, [muteins] mutants and immunogenic fragments, as defined further below.

Please replace the paragraph starting at page 14, line 28, with the following rewritten paragraph:

The present invention also extends to an immunogenic complex as described above wherein the charged antigen is a fragment of an HCV protein. By "fragment" is intended a polypeptide consisting of only a part of the intact full-length protein sequence and structure. The fragment can include a C-terminal deletion and/or an N-terminal deletion of the native polypeptide. An "immunogenic fragment" of a particular HCV protein will generally include at least about 5-10 contiguous amino acid residues of the full-length molecule, preferably at least about 15-25 contiguous amino acid residues of the full-length molecule, and most preferably at least about 20-50 or more contiguous amino acid residues of the full-length molecule, that define an epitope, or any integer between 5 amino acids and the full-length sequence, provided that the fragment in question retains the ability to elicit an immune response as defined below. For example, preferred immunogenic fragments, include but are not limited to fragments of the core protein of HCV that comprise, e.g., amino acids 10-45, 10-53, 67-88, 812-130, 86-100, 120-130, 121-135 and 121-170 of the polyprotein, numbered relative to the HCV-1a sequence present in Choo *et al.*, (1991) *Proc. Natl. Acad. Sci. USA* 88:2451, as well as defined epitopes derived from the c33c region of the HCV polyprotein, as well as any of the other various epitopes identified from the HCV core, E1, E2, NS3 [and] NS4 and NS5 regions. See, e.g., Chien *et al. Proc. Natl. Acad. Sci. USA* (1992) 89:10011-10015; Chien *et al. J. Gastroent. Hepatol.* (1993) 8:S33-39; Chien *et al.* International Publ. No. WO 93/00365; Chien, D.Y. International Publ. No. WO 94/01778; allowed U.S. Patent Application Serial Nos. 08/403,590 and 08/444,818.

Please replace the paragraph starting at page 22, line 5, with the following rewritten paragraph:

Reference throughout this specification to "organic [carrier] complex" should be understood as a reference to any molecule, aggregate or complex of molecules, compound or other entity which, when an antigen is associated with it, facilitates the induction of an immune response, and in particular a cytotoxic T-lymphocyte response, to the antigen. The subject [carrier] complex is "organic" and, in this regard, "organic" should be understood as a compound of carbon whether naturally, recombinantly or synthetically obtained or derived.

In a particularly preferred embodiment the organic [carrier] complex is an adjuvant. By "adjuvant" is meant any molecule, aggregate or complex of molecules, compound or other entity which functions to stimulate, enhance or otherwise up-regulate any one or more aspects of the immune response. For example, the adjuvant may induce inflammation thereby attracting immune response cells to the site of antigen localization. Alternatively, the adjuvant may slowly release the antigen thereby providing on-going stimulation of the immune system.

Please replace the paragraph starting at page 22, line 19, with the following rewritten paragraph:

Examples of charged organic [carriers] complexes which are adjuvants suitable for use in the present invention include, but are not limited to, [saponin,] saponin complexes [,any one or more components] comprising a saponin and a sterol such as cholesterol, [of the] particularly an immunostimulating complex [of] comprising a saponin and a sterol such as the complex of saponin, cholesterol and lipid known as ISCOMATRIX™ [(for example the saponin component), liposomes or oil-in-water emulsions]. (The composition and preparation of ISCOMATRIX™ is described in detail in International Patent Application Number PCT/SE86/00480, Australian Patent Numbers 558258 and 632067 and European Patent Publication No. 0 180 564, the disclosures of which are incorporated herein by reference). [Further examples of adjuvants include, but are not limited to, those detailed in the publications of Cox and Coulter, 1992, 1997 and 1999.] It should be understood that the subject organic [carrier] complex may be naturally occurring or it may be synthetically or recombinantly derived.

Please replace the paragraph starting at page 23, line 1, with the following rewritten paragraph:

Accordingly, the present invention still more preferably provides an immunogenic complex as described above, wherein the charged organic [carrier] complex is an adjuvant.

Please replace the paragraph starting at page 23, line 5, with the following rewritten paragraph:

Preferably, said adjuvant comprises [saponin or] a saponin complex. More preferably, said saponin complex is ISCOMATRIX™.

Please replace the paragraph starting at page 23, line 8, with the following rewritten paragraph:

The organic [carrier] complex of the present invention may also be, in its initial or natural form, negatively charged, positively charged or neutral. Increasing the degree of negative charge (for example, where the organic [carrier] complex is only weakly negatively charged) or converting a neutral or positively charged organic [carrier] complex to a negatively charged organic [carrier] complex may also be achieved by any suitable method known to those skilled in the art. For example, [where the organic carrier is an oil-in-water emulsion, incorporation of any anionic surfactant with a non-polar tail will impart an overall negative charge to the emulsion due to insertion of the tail of the surfactant into the oil droplet which thereby leaves the negatively charged head group exposed.] [T]the negative charge of a saponin complex adjuvant may be increased, for example, by the addition of negatively charged lipid during complex formation.

Please replace the paragraph starting at page 23, line 20, with the following rewritten paragraph:

Example of detergents which can increase the negative charge of a carrier include, but are not limited to cholic acid, deoxycholic acid, taurocholic acid and taurodeoxycholic acid. Examples of lipids which can increase the negative charge of a [carrier] complex include, but are not limited to, phospholipds (preferably phosphatidyl inositol, phosphatidyl serine, phosphatidyl glycerol and phosphatidic acid and most preferably cardiolipin) and bacterial

lipids (preferably monophosphoryl lipid A(MPL) and most preferably diphosphoryl lipid A, such as OM174 as described in International Patent Publication No. WO 95/14026.

Please replace the paragraph starting at page 23, line 29, with the following rewritten paragraph:

Without limiting the present invention in any way, the inventors have determined that where the subject charged organic [carrier] complex and charged antigen are naturally negatively and positively charged, respectively, the object of the invention can be achieved. However, a still more effective immunogenic complex may be achieved if the subject naturally negatively charged organic [carrier] complex is rendered more negatively charged (preferably by addition of cardiolipin or diphosphoryl lipid A).

Please replace the paragraph starting at page 24, line 4, with the following rewritten paragraph:

Accordingly, in one preferred embodiment there is provided an immunogenic complex as described above, wherein the organic complex is a naturally negatively charged adjuvant [which has been modified to increase the degree of its negative charge]. In another aspect, the organic complex may be modified to increase the degree of its negative charge.

Please replace the paragraph starting at page 24, line 16, with the following rewritten paragraph:

The present invention is predicated, in part, on the formation of immunogenic complexes via the electrostatic association, preferably, of a negatively charged organic [carrier] complex with a positively charged antigen. The administration of such a complex to a subject facilitates the induction of a significantly better immune response than would be achieved were the adjuvant and antigen administered simultaneously but in a non-associated

form. In particular, the administration of an antigen associated with an adjuvant, according to the present invention, facilitates the induction of a cytotoxic T-lymphocyte response to the antigen. However, humoral and other cellular responses can also be enhanced.

Please replace the paragraph starting at page 24, line 26, with the following rewritten paragraph:

Generally, in the immunogenic complex of the present invention, the ratio of the charged organic [carrier] complex to the charged antigen, by weight, is in the range of 5:1 to 0.5:1. Preferably, the ratio by weight in approximately 3:1 to 1:1, and more preferably the ratio by weight is 2:1.

Please replace the paragraph starting at page 25, line 13, with the following rewritten paragraph:

Accordingly, another aspect of the present invention relates to a vaccine composition comprising as the active component an immunogenic complex comprising a negatively charged organic [carrier] complex and a charged antigen, which organic [carrier] complex and antigen are electrostatically associated, [and] wherein the organic complex comprises a saponin and a sterol, and wherein the charged antigen [is a polyprotein] comprises one or more polypeptides from a region of Hepatitis C Virus (HCV) [or a fragment thereof, or a fusion protein comprising said polyprotein or a fragment thereof,] selected from the group consisting of core, E1, E2, NS3, NS4a, NS4b, NS5a and NS5b, together with one or more pharmaceutically acceptable carriers and/or diluents.

Please replace the paragraph starting at page 25, line 21, with the following rewritten paragraph:

Preferably, said organic [carrier] complex is an adjuvant, and even more preferably a [saponin or a] saponin complex. Preferably said saponin complex is ISCOMATRIX™.

Please replace the paragraph starting at page 26, line 17, with the following rewritten paragraph:

The vaccine compositions may also include further adjuvants to enhance effectiveness of the composition. Suitable adjuvants include, but are not limited to those detailed in the publications of Cox and Coulter, 1992, 1997 and 1999 (supra), including: (1) aluminum salts (alum), such as aluminum hydroxide, aluminum phosphate, aluminum sulfate, etc.; (2) oil-in-water emulsion formulations (with or without other specific immunostimulating agents such as muramyl peptides (see below) or bacterial cell wall components), such as for example (a) MF59 (PCT Publ. No. WO 90/14837), containing 5% Squalene, 0.5% Tween 80, and 0.5% Span 85 (optionally containing various amounts of MTP-PE (see below), although not required) formulated into submicron particles, (b) SAF, containing 10% Squalene, 0.4% Tween 80, 5% pluronic-blocked polymer, and thr-MDP (see below) either microfluidised into a submicron emulsion or vortexed to generate a large particle size emulsion, and (c) Ribi™ adjuvant system (RAS), (Ribi Immunochem, Hamilton, MT) containing 2% Squalene, 0.2$ Tween 80, and one or more bacterial cell wall components from the group consisting of monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL+CWS (Detox™); (3) saponin adjuvants such as Stimulon™ (Cambridge Bioscience, Worcester, MA); (4) Complete Freund's Adjuvant (CFA) and Incomplete Freund's Adjuvant (IFA); (5) cytokines, such as interleukins (e.g., IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12, etc.), interferons (e.g. gamma interferon), macrophage colony stimulating factor (M-CSF), tumor necrosis factor (TNF), etc.; (6) detoxified mutants of a bacterial ADP-ribosylating toxin such as a cholera toxin (CT), a pertussis toxin (PT), or an *E. coli* heat-labile toxin (LT), particularly LT-K63, LT-R72, CT-S109, PT-K9/G129; see, e.g. WO 93/13302 and WO 92/19265; (7) other substances that act as immunostimulating agents to enhance the effectiveness of the composition; and (8) microparticles with adsorbed macromolecules, as

described in International Patent Application No. PCT/US99/17308. Alum and MF59 are preferred.

Please insert the following new heading on page 32, line 4:

"EXAMPLES 1 TO 6"

Please replace the paragraph starting at page 43, line 5, with the following rewritten paragraph:

Because vaccination with recombinant HCV envelope proteins and adjuvant can, at least in some instances, influence the outcome of infection and disease (Choo *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:1294), we investigated whether the Core-ISCOM above could serve as an adjuvant for other HCV polypeptides, such as the heterodimeric envelope protein E1E2. To that end, mice (10 animals per group) were immunized with 2μg of soluble E1E2 protein alone, or 2μg of soluble E1E2 in the presence of the adjuvant MF59, or in the presence of 2μg of Core-ISCOM. As shown in Figure 8, mice immunized with E1E2 alone had no significant anti-E2 antibody titer. In contrast, mice immunized with E1E2 + Core-ISCOM had a significant anti-E2 antibody titer after three immunizations, and these titers were comparable to those observed in mice immunized with E1E2 + MF59. Furthermore, the 'quality' of antibody elicited in mice immunized by E1E2 + MF59 and E1E2 + Core-ISCOM appeared to be comparable with the antibody titers that could inhibit the binding of HCV-1a E2 to the HCV putative receptor CD81 in both groups of mice (Figure [9] 8).

On page 47, please replace footnote c with the following:

epitope recognized was aa: 121-[130]135 (KVIDTLTCGFADLMG).